Modeling Ovarian Folliculogenesis: Morphogenesis and Population Dynamics

Celine Bonnet, Keltoum Chahour, Frederique Clement, Marie Postel, Frédérique Robin, Romain Yvinec

Modeling ovarian folliculogenesis : Morphogenesis and population dynamics

C. Bonnet [1], K. Chahour [2], F. Clément [3], M. Postel [4], F. Robin [3] and R. Yvinec [5]
[1] Ecole Polytechnique [2] Université Côte d'Azur [3] Inria Paris-Saclay [4] Sorbonne Université [5] INRA Tours

Introduction

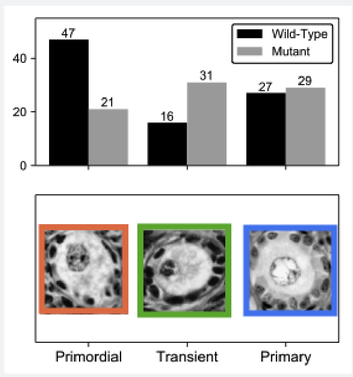
We present stochastic population dynamic models applied to several situations to understand ovarian folliculogenesis
- ◇ Somatic cell population dynamics in a single follicle (either in the activating or basal growing phase)
- ◇ Whole follicle population dynamics during the reproductive lifespan

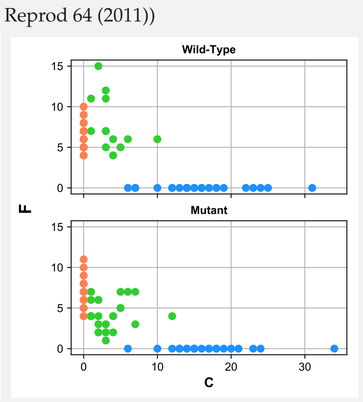
Cell dynamics in an activating follicle

Somatic cell transition and proliferation during follicle activation

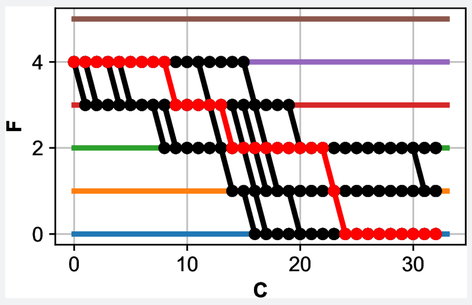
Key questions: What are the kinetics of follicle activation ?
Are transition and proliferation concomitant ?

Data: Cell counts (Lundy et al., J. Reprod. Fertil., 115 (1999); Wilson et al. Biol Reprod 64 (2011))



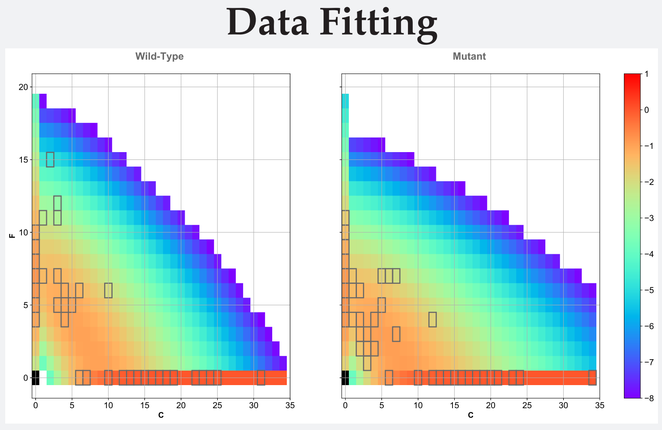


Model: Flattened (F) and Cuboidal (C) cell dynamics



Stochastic Nonlinear Model	Cell events	Rate
Spontaneous transition	$(F,C) \to (F-1, C+1)$	αF
Auto-amplified transition	$(F,C) \to (F-1, C+1)$	$\beta \frac{FC}{F+C}$
Cuboidal Proliferation	$(F,C) \to (F, C+1)$	γC
Self-renewing asymmetric divisions	$(F,C) \to (F, C+1)$	δF

Data Fitting



Results: see [3]

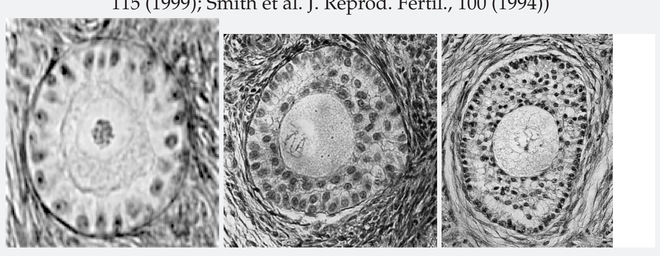
- Clear separation between transition and proliferation in Wild-type.
- Auto-amplification is not mandatory, especially for the Mutant dataset

Cell dynamics in a growing follicle

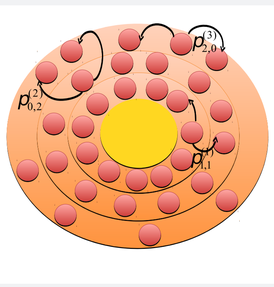
Somatic cell proliferation during basal follicle growth

Key questions: What is the rate of growth ?
Is proliferation oocyte-dependent ?

Data: Total cell numbers, Oocyte and Follicle diameters at three time points (Lundy et al., J. Reprod. Fertil., 115 (1999); Smith et al. J. Reprod. Fertil., 100 (1994))

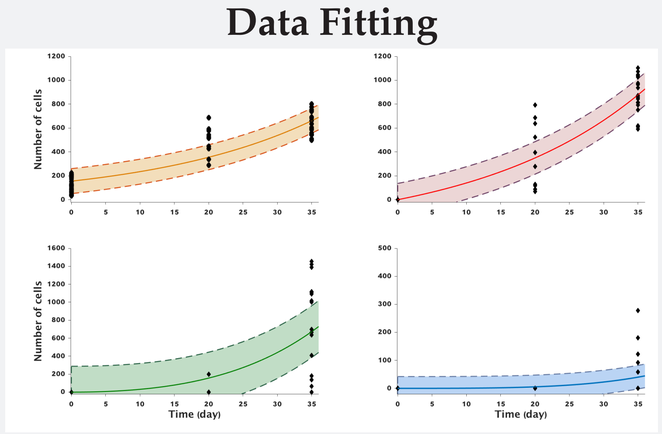


Model: Cell proliferation and repartition in successive layers



Stochastic Linear Model	Cell events	Rate
Both daughter cells stay on mother's layer	$N^j \to 2N^j$	$p^j_{2,0} b_j N^j$
One daughter cell into next mother's layer	$N^j \to N^j + N^{j+1}$	$p^j_{1,1} b_j N^j$
Both daughter cells into next mother's layer	$N^j \to 2N^{j+1}$	$p^j_{0,2} b_j N^j$

Data Fitting



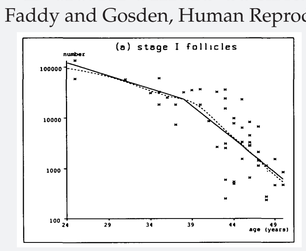
Results: see [2]
Data are compatible with
- an exponential growth phase.
- a layer-dependent growth rate is decreasing with oocyte distance

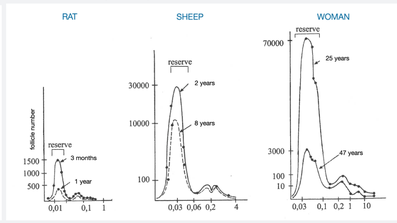
Whole follicle population dynamics

Nonlinear interactions between follicular populations

Key questions: How a quasi-stable maturity repartition is achieved ?
What is the role of nonlinear interactions ?

Data: Follicle counts according to maturity class
Faddy and Gosden, Human Reproduction, 10 (1995); Thibault and Levasseur 2001



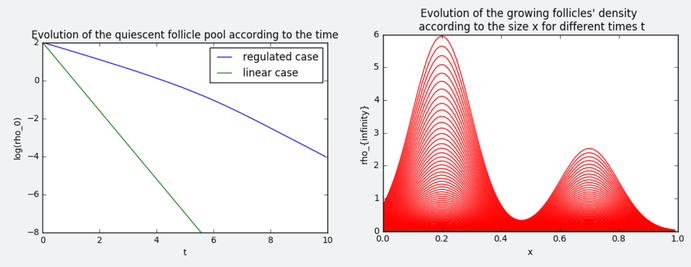


Model: Population-dependent follicle maturity and atresia

$$\cdots \xrightarrow{\lambda_{j-1}} F_{j-1} \xrightarrow{\lambda_j} \cdots$$
$$\downarrow \mu_j$$
$$\emptyset$$

Stochastic Nonlinear Model	Follicle events	Rate
Follicle activation	$F_0 \to F_1$	$\varepsilon \frac{\lambda_0}{1+K\sum_{j=1}^d a_j F_j} F_0$
Follicle maturation	$F_j \to F_{j+1}$	$\lambda_j F_j$
Follicle atresia	$F^j \to \emptyset$	$\mu_j F_j$

Qualitative agreement



Results: see [1]

- Time-scale separation explains quasi-stable maturity repartition.
- Removal of activation inhibition explains acceleration of reserve exhaustion

Mathematical Toolbox

- (Structured) Population dynamics model: deterministic and stochastic models.
- Long-time and asymptotic analysis, time-scale separation.
- Transient analysis: analytical and numerical solutions, first passage time.
- Statistical methods: parameter estimation and identifiability analysis.

Conclusion and Perspective

Mathematical modeling helps:
- ◇ to test different follicle growth scenario and make prediction
- ◇ to challenge biological knowledge on follicle dynamics.

Current study and future projects will focus on different scales:
- ⋆ **Intra-cellular scale**: FSHR signaling network and its role in follicle selection (for a review of gonadotropin signaling models, see [5]).
- ⋆ **Follicle scale**: coupling cell dynamics with biomechanics model to model antrum formation (extending and revisiting previous model [4]).
- ⋆ **Ovarian scale**: Complement follicle population dynamics with (i) ovarian reserve formation and (ii) ovarian cycle dynamics.
  Comparative physiology approaches will also be taken into account.

References

[1] C. Bonnet, K. Chahour, F. Clément, M. Postel, and R. Yvinec. Multiscale population dynamics in reproductive biology: Singular perturbation reduction in deterministic and stochastic models. *Arxiv preprint: 1903.08555v1*, Mar. 2019.

[2] F. Clément, F. Robin, and R. Yvinec. Analysis and Calibration of a Linear Model for Structured Cell Populations with Unidirectional Motion: Application to the Morphogenesis of Ovarian Follicles. *SIAM Journal on Applied Mathematics*, 79(1):207–229, Jan. 2019.

[3] F. Clément, F. Robin, and R. Yvinec. Stochastic nonlinear model for somatic cell population dynamics during ovarian follicle activation. *Arxiv preprint: 1903.01316v1*, Mar. 2019.

[4] F. Clément, P. Michel, D. Monniaux, and T. Stiehl. Coupled somatic cell kinetics and germ cell growth: multiscale model-based insight on ovarian follicular development. *Multiscale Modeling & Simulation*, 11(3):719–746, 2013.

[5] R. Yvinec, P. Crépieux, E. Reiter, A. Poupon, and F. Clément. Advances in computational modeling approaches of pituitary gonadotropin signaling. *Expert Opinion on Drug Discovery*, 13(9):799–813, Sept. 2018.

Acknowledgement: We thank Ken McNatty for providing experimental datasets and Danielle Monniaux for helpful discussion (and histological images!).